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(54) **HIGH VISCOSITY EMBOLIZING COMPOSITIONS**

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(58) **Field of Search** 424/9.455, 9.4, 424/9.45, 9.41, 1.29, 1.65, 422, 426, 423; 604/264, 49; 514/708, 546

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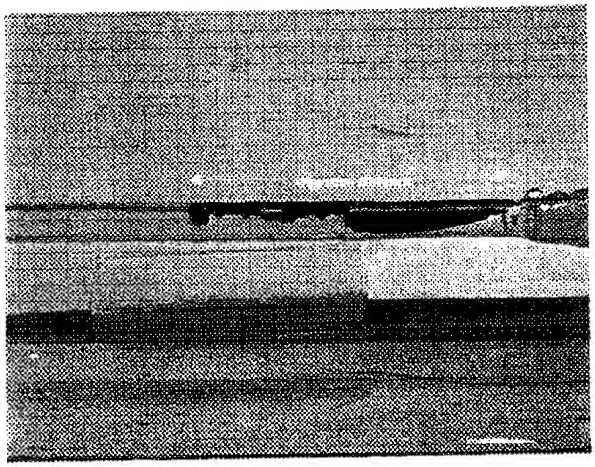
(57) **ABSTRACT**

Disclosed are novel compositions for embolizing blood vessels which are particularly suited for treating vascular lesions via catheter delivery.

15 Claims, 1 Drawing Sheet



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C., an increase in viscosity correlates with a reduction in migration distance.

The above data further indicates that an increase in concentration of polymer alone without a corresponding increase in viscosity does not provide for reduced migration distances. For example, in Table II, the first and last compositions have approximately equal viscosities but the last composition has a 10 fold higher concentration of polymer. Nevertheless, the latter composition does not reduce the migration distance as compared to the first composition.

Example 5

The purpose of this example is to still further demonstrate that reduced migration of the formed precipitate can be achieved by increasing the viscosity of the composition. The procedures used in this example were similar to those of Example 4.

The results of this test are set forth in Table IV below:

TABLE IV

Polymer	Concentration (wght. %)	Viscosity (cSt at 40° C.)	Average Migration Distance (in mm)^2	Standard Deviation
EVOH-3	4.6	18	33.2	6.18
EVOH	6.2	34	28.2	4.15
EVOH	9.2	90	24.2	4.92
EVOH	12.3	200	24.6	3.44
EVOH	15.4	500	23.2	2.59
EVOH	23.1	2500	20.0	2.92

From the foregoing description, various modifications and changes in the above described methods will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

What is claimed is:

1. A composition capable of embolizing an aneurysm at a vascular site comprising:

(a) a biocompatible polymer at a concentration of from about 12 to about 50 weight percent based on the total weight of the composition;

(b) a biocompatible contrast agent wherein a sufficient amount of said contrast agent is employed in said composition to effect visualization in vivo; and

(c) a biocompatible solvent which solubilizes said biocompatible polymer wherein sufficient amounts of said polymer are employed in said composition such that, upon delivery to a vascular site, a polymer precipitate forms which embolizes said vascular site; and further wherein the biocompatible polymer has a molecular weight and/or concentration sufficient to impart to the composition a viscosity of at least about 150 cSt at 40° C.

2. A composition capable of embolizing an aneurysm at a vascular site comprising:

(a) a biocompatible polymer at a concentration of from about 12 to about 50 weight percent;

(b) a biocompatible contrast agent at a concentration of from about 10 to about 40 weight percent; and

(c) a biocompatible solvent from about 10 to 88 weight percent wherein the weight percents of the biocompatible polymer, contrast agent and biocompatible solvent are based on the total weight of the composition; and further wherein the biocompatible polymer has a molecular weight and/or concentration sufficient to impart to the composition a viscosity of at least about 150 cSt at 40° C.

3. The composition according to claim **1** or claim **2**, wherein said composition has a viscosity of at least about 200 cSt at 40° C.

4. The composition according to claim **3**, wherein said composition has a viscosity of at least about 500 cSt at 40° C.

5. The composition according to claim **4**, wherein said composition has a viscosity of from about 500 to 5,000 cSt at 40° C.

6. The composition according to claim **1** or claim **2** wherein said composition has a migration distance of less than 25 mm.

7. The composition according to claim **1** or claim **2** wherein said biocompatible solvent is selected from the group consisting of ethyl lactate, dimethylsulfoxide, ethanol and acetone.

8. The composition according to claim **7** wherein said biocompatible solvent is dimethylsulfoxide.

9. The composition according to claim **1** or claim **2** wherein said contrast agent is a water insoluble contrast agent.

10. The composition according to claim **9** wherein said water insoluble contrast agent is selected from the group consisting of tantalum, tantalum oxide, tungsten and barium sulfate.

11. The composition according to claim **10** wherein said contrast agent is tantalum.

12. The composition according to claim 1 or claim **2** wherein said contrast agent is a water soluble contrast agent.

13. The composition according to claim 1 or claim **2** wherein said biocompatible polymer is a non-biodegradable, biocompatible polymer.

14. The composition according to claim **13** wherein said non-biodegradable, biocompatible polymer is selected from the group consisting of cellulose acetates, ethylene vinyl alcohol copolymers, hydrogels, polyacrylonitrile, polyvinylacetate, cellulose acetate butyrate, nitrocellulose, copolymers of urethane/carbonate, copolymers of styrene/maleic acid, and mixtures thereof.

15. The composition according to claim **14** wherein said biocompatible polymer is an ethylene and vinyl alcohol copolymer.

* * * * *

When high pressure is employed to effect delivery, the catheter preferably is rated to 100 psi use pressure to ensure against rupture.

Utility

The methods, devices, and compositions described herein are useful in embolizing mammalian blood vessels which, in turn, can be used to prevent/control bleeding (e.g., organ bleeding, gastrointestinal bleeding, vascular bleeding, bleeding associated with an aneurysm) or to ablate diseased tissue (e.g., tumors, etc.). Accordingly, the invention finds use in human and other mammalian subjects requiring embolization of blood vessels.

It is contemplated that the compositions can be employed as a carrier for a compatible pharmaceutically active compound wherein this compound is delivered in vivo for subsequent release. Such compounds include by way of example only antibiotics, anti-inflammatory agents, chemotherapeutic agents, anti-angiogenic agent, and the like.

The following examples are set forth to illustrate the claimed invention and are not to be construed as a limitation thereof.

EXAMPLES

Unless otherwise stated, all temperatures are in degrees Celsius. Also, in these examples and elsewhere, the following abbreviations have the following meanings:

cc =	cubic centimeters
cSt =	centistokes
DMSO =	dimethylsulfoxide
EVOH =	ethylene vinyl alcohol copolymer
g =	gram
mL =	milliliter
mm =	millimeter
μm =	micron

Example 1

This example illustrates the preparation of compositions of this invention having a high viscosity. Specifically, an EVOH polymer composition was prepared as follows:

17.5 weight % EVOH polymer having a 48 mole % ethylene, with a molecular weight of approximately 136,000

30 weight % micronized tantalum

52.5 weight % anhydrous DMSO

Viscosity=approximately 1100 cSt at 40° C.

After dissolution of the polymer at 50° C. in DMSO with stirring, micronized tantalum (average size 3 μm) was then added. The resulting composition was then heated for approximately 5 minutes at 70° C. in a heated block, removed and then shaken in a vortex mixer for approximately 20 minutes at room temperature to disperse the insoluble tantalum and to provide for a uniform suspension of the tantalum in the polymer/solvent solution. The composition was replaced into the 70° C. heated block and rewarmed for a minimum of 10 minutes before filling a syringe and injection.

Example 2

An experimental side wall venous pouch aneurysm was created in the left carotid artery of a 25 kg juvenile domestic swine. A femoral access was made immediately thereafter and a microcatheter (MicroTherapeutics Rebar Microcatheter ™) was placed near the aneurysm site with the aid of a 0.014 inch guide wire (Microtherapeutics Silver Speed ™). Through another femoral access, a microballoon catheter (Microtherapeutics Equinox microballoon catheter) was also placed at the aneurysm site.

The microcatheter was then placed through the aneurysm neck into the aneurysm sac at least one third toward the fundus of the aneurysm. The microballoon bridged the neck of the aneurysm. The microcatheter was flushed with 5 mL of saline and then primed with 0.25 cc of DMSO. A threaded syringe filled with the composition of Example 1 (as described above) was then connected to an interface needle device (as described above). The threaded syringe interface needle device assembly was then connected to the microcatheter.

The balloon was then inflated to completely occlude blood flow through the carotid artery and seal the aneurysm neck. Approximately 0.2 mL of the composition of Example 1 was injected at a steady rate not exceeding 0.1 mL per minute. The composition was kept warm at approximately 40° C. during this process.

The balloon was deflated for two minutes to allow the solvent to dissipate. The balloon was then re-inflated and an additional 0.2 mL of the composition was,again injected through the delivery catheter with use of the screw syringe device. The balloon was allowed to remain inflated for 5 minutes. The process of balloon inflation, injection of composition and balloon deflation was repeated until the aneurysm was completely filled to the neck as determined by fluoroscopy. The delivery microcatheter was then withdrawn, the balloon was deflated and the microballoon catheter withdrawn.

From the foregoing description, various modifications and changes in the above described methods will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

What is claimed is:

1. A method for embolizing a vascular site, said method comprising:

(a) preparing an embolic composition comprising (1) a biocompatible polymer, (2) a biocompatible solvent which solubilizes said polymer, and (3) a water insoluble contrast agent which is suspended in said composition, wherein said embolic composition has a viscosity of at least 150 centistokes at 40° C.,

(b) heating and mixing the embolic composition to at least 40° C. to form a uniform suspension,

(c) transferring the heated embolic composition to a delivery catheter having a proximal end and a distal end, wherein the distal end of the delivery catheter is positioned at the vascular site to be embolized, and

(d) injecting the heated embolic composition into said vascular site in sufficient amounts to embolize said vascular site.

2. The method according to claim **1** wherein the composition transferred in (c) is maintained at a temperature above 40° C.

3. The method according to claim **1** wherein, prior to (d) above, a blood flow attenuating device is inserted immediately upstream the ejection port of said catheter.

4. The method according to claim **3** wherein said blood flow attenuating device is an inflatable microballoon which permits both normal and attenuated blood flow depending upon whether the microballoon is deflated or inflated.

5. The method according to claim **1**, wherein said composition has a viscosity of at least 200 centistokes at 40° C.

6. The method according to claim **5**, wherein said composition has a viscosity of at least 500 centistokes at 40° C.

7. The method according to claim **6**, wherein said composition has a viscosity of from at least 500 to 5,000 centistokes at 40° C.

8. The method according to claim **1**, wherein the concentration of biocompatible polymer employed in said composition is from 6 to 50 weight percent.

9. The method according to claim **8**, wherein the concentration of biocompatible polymer employed in said composition is from 8 to 30 weight percent.

10. The method according to claim **1** wherein said biocompatible solvent is selected from the group consisting of ethyl lactate, dimethylsulfoxide, ethanol and acetone.

11. The method according to claim **10** wherein said biocompatible solvent is dimethylsulfoxide.

12. The method according to claim **1** wherein said water insoluble contrast agent is selected from the group consisting of tantalum, tantalum oxide, tungsten and barium sulfate.

13. The method according to claim **12** wherein said contrast agent is tantalum.

14. The method according to claim **1** wherein said biocompatible polymer is a non-biodegradable, biocompatible polymer.

15. The method according to claim **14** wherein said non-biodegradable, biocompatible polymer is selected from the group consisting of cellulose acetates, ethylene vinyl alcohol copolymers, hydrogels, polyacrylonitrile, polyvinylacetate, cellulose acetate butyrate, nitrocellulose, copolymers of urethane/carbonate, copolymers of styrene/maleic acid, and mixtures thereof.

16. The method according to claim **15** wherein said biocompatible polymer is an ethylene and vinyl alcohol copolymer.

17. The method according to claim **1** wherein said biocompatible polymer is a biodegradable, biocompatible polymer.

18. The method according to claim **1** wherein said catheter has a length of at least 50 cm.

19. A method for embolizing a vascular site, said method comprising:

(a) preparing an embolic composition comprising (1) a biocompatible polymer, (2) a biocompatible solvent which solubilizes said polymer, and (3) a water insoluble contrast agent which is suspended in said composition, wherein said embolic composition has a viscosity of at least 150 centistokes at 40° C.,

(b) heating and mixing the embolic composition to at least 40° C. to form a uniform suspension,

(c) positioning the distal end of a delivery catheter having a proximal end and a distal end into the vascular site to be embolized,

(d) positioning a flow arresting device at the vascular site to be embolized,

(e) connecting the delivery catheter to the embolic composition prepared in (a) above under conditions wherein the temperature of the composition is above room temperature,

(f) activating the flow arresting device at the vascular site to be embolized such that the activated device reduces blood flow through the vascular site to be embolized but does not occlude the delivery catheter,

(g) injecting said composition into said vascular site under conditions wherein the temperature of said composition at the ejection port is in equilibrium with the body temperature of said mammal,

(h) deactivating the flow arresting device to permit sufficient blood flow through said vasculature to be embolized such that removal of the biocompatible solvent is facilitated and oxygenated blood is delivered to the tissue distal to said flow arresting device, and

(i) repeating steps (f)–(h) as necessary to effect embolization of said vascular site.

20. The method according to claim **19** wherein the composition transferred in (e) is maintained at a temperature above 40° C.

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